# Severe mucitis after sublingual administration of tetrahydrobiopterin in a patient with tetrahydrobiopterin-responsive phenylketonuria

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SHORT REPORT

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# Severe mucitis after sublingual administration of tetrahydrobiopterin in a patient with tetrahydrobiopterin-responsive phenylketonuria

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Tetrahydrobiopterin ($BH_4$) is the cofactor for phenylalanine hydroxylase (PAH) and is essential to treat different forms of hyperphenylalaninaemia, i.e. patients with defects in the biosynthesis of $BH_4$, but also in the PAH gene [1, 4,5]. Responsiveness of mutant PAH to $BH_4$ administration relies on a chemical chaperon effect of $BH_4$ preventing PAH from protein misfolding and inactivation [6], but several other mechanisms may also be involved [2]. Recently, we reported that sublingual administration of $BH_4$ tablets in a single control person resulted in 58%–67% higher plasma $BH_4$ concentrations than the usual oral route [3]. Drawbacks included rapid decomposition of tablets, acidic taste, and increased salivation. Since sublingual application could reduce therapy costs, orange flavoured artificially sweetened $BH_4$ pastilles were tested on four healthy volunteers and a child with mild phenylketonuria (PKU).

$BH_4$ (Schircks, Switzerland) was administered to four healthy male volunteers (age 28–57 years) on 2 subsequent days either as tablets (50 mg) or pastilles (100 mg, containing 5 mg aspartame and orange aroma) with a 1 week wash-out between the two trials. Blood was collected before, and 1, 2, 3, and 4 h after administration. An 8-year-old patient with mild PKU (genotype P281L/R261Q) who was already on regular $BH_4$ therapy was treated with $BH_4$ pastilles (sublingually, 12 mg/kg/day; bid) in addition to P-AM 2 formula for 2 weeks. Written consensus was obtained from the family.

In the four healthy male volunteers, total biopterin values before and up to 4 h after oral and sublingual administration were compared (Fig. 1A). No statistically significant difference between oral and sublingual administration was observed. Pterin concentrations increased after both oral and sublingual administration, reflecting instability of $BH_4$ in blood. The ratio of pterin to cumulated biopterin and pterin ranged between 22.8% and 33.5%. Summing biopterin and pterin instead of total biopterin did not alter the ratio between oral and sublingual administration (data not shown).

Changing from standard therapy to sublingual administration in a child with mild PKU resulted in almost unchanged plasma phenylalanine concentrations (Fig. 1B). After 2 weeks of twice daily sublingual $BH_4$ administration, the patient complained of a painful prickling sensation at the tip of the tongue. He nevertheless continued the treatment for a further 10 days, moving the tablets in his mouth from one side to the other, which resulted in severe mucitis. His condition normalised rapidly upon discontinuation of the sublingual form. No mucitis appeared in healthy volunteers.

A clinical trial with sublingual $BH_4$ in a patient with mild PKU failed despite pharmacological effectiveness on blood phenylalanine levels because of an adverse pastille-related side-effect. Formulation of buffered tablets approaching neutral pH and further investigations on $BH_4$ metabolism and pharmacokinetics are needed.

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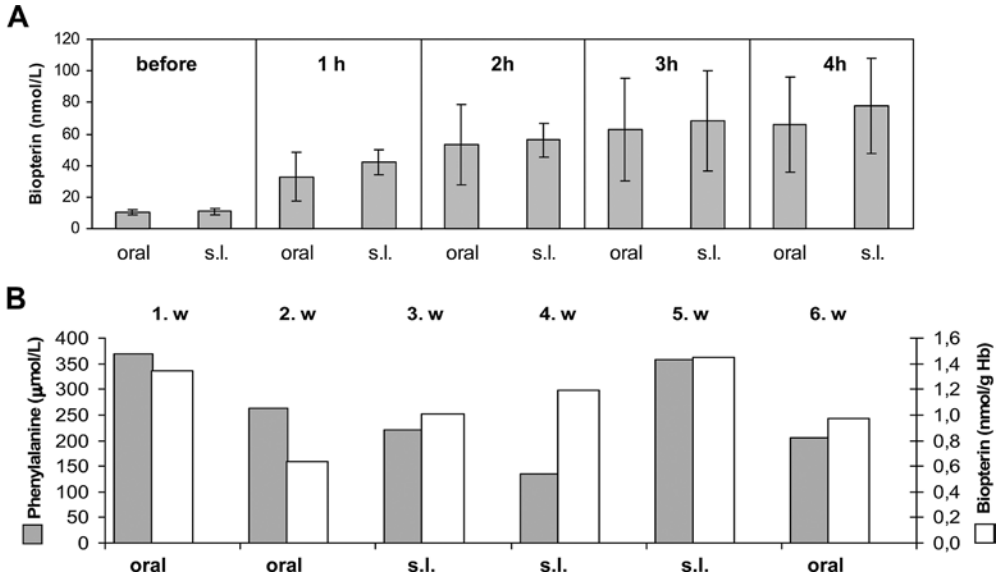


**Fig. 1** **A** Comparison of total plasma biopterin levels (median ± SD) after oral or sublingual administration of $BH_4$ (2 mg/kg) in four healthy volunteers at different time points. **B** Dried blood spot phenylalanine ( *solid squares*) and biopterin ( *open squares*) measured 3 h after oral (15 mg/kg) or sublingual (12 mg/kg) administration of $BH_4$ in a patient with mild PKU ( *s.l.*sublingual)

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